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(57) Abstract

A pharmaceutical aerosol formulation, suitable for administration by oral or nasal inhalation, containing a suspension of particulate budesonide, hydrofluoroalkane propellant and, optionally, additional hydrofluoroalkane propellants, surfactant selected from oleic acid, sorbitant oleates and lecithin, and adjuvant have a Kauri–butanol value of at least 10.

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MEDICINAL AEROSOL FORMULATIONS COMPRISING BUDESONIDE

This invention relates to medicinal aerosol formulations and in particular to aerosol formulations containing budesonide which are suitable for administration to the respiratory system of a patient.

Pharmaceutical suspension aerosol formulations are known which use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

Chlorofluorocarbons (CFCs), however, have been implicated in the destruction of the ozone layer and their production is being phased out. Hydrofluoroalkanes, such as hydrofluoroalkane 134a (HFA 134a, 1,1,1,2-tetrafluoroethane) and hydrofluoroalkane 227 (HFA 227, 1,1,1,2,3,3,3-heptafluoropropane), are viewed as being more ozone friendly than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressures suitable for use in aerosols.

W091/04011, W091/11495, W091/11496, W093/11745, W093/11747, W094/21228, W095/15151, W096/9816, W096/9831, EP-A-0372777, EP-A-0384371, EP-A-0518600, EP-A-0518601, EP-A-0550031, EP-A-O587790 and US-A-5492688 disclose aerosol formulations in which the propellant comprises a hydrofluoroalkane.

EP-A-0605578 discloses pharmaceutical aerosol compositions comprising a liquefied hydrofluoralkane, a powdered medicament and a polymer, soluble in the hydrofluoroalkane, having recurring structural units selected from amide containing units and carboxylic acid ester containing units. One formulation consists of HFA 227, budesonide and a polyvinylpyrrolidone/vinyl acetate copolymer and a further formulation additionally comprises polyethylene glycol.

W093/18746 discloses a pharmaceutical aerosol formulation consisting of HFA 227, budesonide, 1% by weight polyoxyethylene-25-glyceryl-trioleate and 1% by weight ethanol.

EP-A-0504112 discloses inter alia a formulation comprising 0.312% budesonide, 0.039% Myvacet 9-45, 1.171% Tween 60, 11.50% ethanol and 86.978% HFA 227. The ethanol content of this formulation is sufficient to dissolve a substantial proportion of the budesonide and is likely to exhibit crystal growth of budesonide particles.

W094/21229 discloses formulations comprising 0.03% particulate budesonide, 0.05% dispersing aid and 99.92% propellant which was either HFA 134a or HFA 227. The dispersing aids are derived from acetyl-oligo-L-lactic acids. The ingredients were homogenized using ultrasound. After storage, each formulation was shaken by hand then observed on standing. Each of the suspensions is said to flocculate within 5 seconds after shaking ceased.

Suspension formulations of budesonide have a propensity to rapidly form coarse flocs upon dispersion and redispersion which may deleteriously affect dosage reproducibility. There is also a tendency for budesonide to deposit from suspension onto the walls of the container.

The teaching of the state of the art does not provide a ready solution to these problems.

According to one aspect of the present invention there is provided a pharmaceutical aerosol formulation suitable for administration to a patient by oral or nasal inhalation consisting of a suspension of particulate budesonide, a hydrofluoroalkane propellant and optionally one or more of:

(i) one or more additional hydrofluoroalkane propellants

(ii) surfactant selected from oleic acid, sorbitan oleates and lecithin, and

(iii) adjuvant having a Kauri-butanol value of at least 10.

It has been found that it is possible to achieve stable suspensions of particulate budesonide by employing up to 3% of an adjuvant having a Kauri-butanol value greater than 10, e.g., ethanol. In such formulations, the level of adjuvant is selected to decrease the propensity for rapid formation of coarse flocs and for deposition of drug on manufacturing equipment and on the internal surfaces of the container closure system of the inhaler. However, the levels are not so high

as to cause significant solubilization of drug, leading to problems of chemical degradation and particle size increase on storage.

According to a further aspect of the present invention there is provided a pharmaceutical aerosol formulation suitable for administration to a patient by oral or nasal inhalation consisting essentially of a suspension of budesonide particles in a mixture of hydrofluoroalkane propellants and optionally one or more excipients selected from:

(i) an adjuvant having a Kauri-butanol value of at least 10,

(ii) the combination of an adjuvant (i) and a surfactant selected from oleic acid, sorbitan oleates and lecithin, and

such that the liquid mixture has a density at 20°C substantially equal to the density of budesonide.

It has been found that it is possible to achieve stable suspensions of particulate budesonide by employing a mixture of HFA propellants by matching the density of the propellant mixture to be substantially identical to the density of budesonide. Such formulations are referred to herein as "density matched". The particles preferably have an average size in the range 1 to 10μm.

In addition to its use for the control of asthma, budesonide is particularly suited for nasal delivery in the treatment of allergic rhinitis. Formulations for this application preferably do not contain high levels of ethanol in order to avoid irritation of the nasal mucosa. Levels of about 1% by weight ethanol have been found not to produce irritation.

Formulations of the invention exhibit substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, are substantially and readily redispersible, and upon redispersion do not flocculate so quickly as to prevent reproducible dosing of the drug.

It has been found that budesonide particles will sink when suspended in 100% HFA 134a but float when suspended in 100% HFA 227.

It has been found that it is possible to match the density of budesonide using a propellant mixture of HFA's, particularly a mixture of HFA 134a and HFA 227.

Suitable propellant mixtures comprise from 15 to 35%, HFA 227 and correspondingly 65 to 85% by weight HFA 134a.

Although density matched mixtures of HFA propellants provide improved formulations of suspended budesonide compared with the use of single propellants, such mixtures do not necessarily prevent the formation of large flocs or prevent drug deposition on the walls of the container or equipment used in preparing the formulation. It has been found that the presence of an adjuvant having a Kauri-butanol value of at least 10 may improve the properties of both density matched and other formulations of suspended budesonide. The preferred adjuvant is ethanol, but other adjuvants such as isopropyl alcohol and polyethylene glycol may be used. The adjuvant is preferably present in a proportion which does not lead to excessive crystal growth or produce irritation when inhaled, particularly when inhaled intranasally.

In addition, small amounts of surfactant, preferably from 0.0005 to 0.01% may provide improved properties, e.g., preventing particles adhering to surfaces and providing lubrication for valve components in contact with the formulation. The surfactant is selected from oleic acid, lecithin and sorbitan oleates, e.g., sorbitan monooleate, sorbitan sesquioleate and sorbitan trioleate. The preferred surfactant is oleic acid.

The budesonide is generally present to provide a dose of from 1 to 8 mg/ml of formulation. Exemplary doses are 1, 2, 4 and 8 mg/ml. Such doses are achieved using a concentration of budesonide of from about 0.075 to 0.66% by weight of the formulation depending upon the precise formulation.

Preferred formulations in accordance with the invention consist of:

particulate budesonide
oleic acid
ethanol
HFA 134a
HFA 227

It is conventional practice when preparing aerosol formulations to mix the drug with the highest boiling point material and thereafter mix with the propellant.

However, when making the formulations of the present invention it is important to ensure the budesonide does not come into contact with high concentrations, e.g., above 5% w/w, of ethanol since the drug would dissolve leading to instability and crystal growth problems in the final formulation. Preferably the maximum concentration of ethanol during formulation is less than 1%.

When preparing formulations of the invention with a content of up to 1% w/w ethanol, the concentration of ethanol at any stage in the presence of budesonide must be maintained no higher than this level. A procedure for preparing a budesonide suspension formulation by cold-filling is as follows:

a) Add all of the formulation quantity of HFA 134a and half of the formulation quantity of HFA 227 to a batching vessel.

b) Prepare a first concentrate containing any surfactant and at least 85% of the formulation quantity of ethanol. Add this to the batching vessel.

c) Prepare a second concentrate containing the other half of the formulation quantity of HFA 227 and the remainder of the ethanol (i.e., no more than 1% w/w of the second concentrate), and add the micronized drug while mixing under high shear. Add the second concentrate to the batching vessel.

The invention will now be described with reference to the following Examples which employed micronized budesonide.

Examples 1 to 9

Formulations were prepared using HFA 134a as propellant. Particulate budesonide was present at 0.33% by weight optionally with ethanol and surfactant as reported in the following table.

Example		Surfactant	
	% Ethanol	% Oleic Acid	% Span 85
1	0	0	0
2	1	0	0
3	1	0.01	0
4	1	0.05	0
5	2.5	0	0
6	2.5	0.01	0
7	2.5	0.05	0
8	2.5	0	0.002
9	2.5	0	0.010

All formulations gradually sedimented.

Examples 5 to 9 were examined for particle size over a one month period of storage in a 4°C/40°C temperature cycling chamber.

Example 5 started with a larger particle size than Examples 6 to 9, indicating poorer dispersion. However, there was no significant change in particle size on storage. Examples 6 to 9 all showed a slight increase in particle size on storage, but not sufficient to equal the particle size of Example 5.

Examples 10 and 11

The following formulations were prepared in which the amounts are expressed in % w/w:

Example	10	11
Budesonide	0.280	0.653
HFA 227	99.720	
HFA 134a	-	99.347

The formulation of Example 10 exhibited small flocs almost immediately which gradually floated to the surface.

The formulations of Example 11 exhibited small flocs almost immediately which gradually sank.

Examples 12 to 22

The formulations reported in the following Tables were prepared in which the amounts are expressed in % w/w:

Example	12	13	14	15	16
Budesonide	0.316	0.316	0.318	0.660	0.660
Oleic Acid	0.005	0.005	0.005	0.010	0.005
Ethanol	1.000	3.000	5.000	1.000	1.000
HFA 227	29.902	29.296	28.690	-	-
HFA 134a	68.777	67.383	65.987	98.330	98.335

Example	17	18	19	20	21	22
Budesonide	0.632	0.632	0.632	0.329	0.316	0.316
Oleic Acid	-	-	0.005	0.005	-	0.001
Ethanol	-	0.994	1.000	1.000	1.000	1.000
HFA 227	25.836	29.810	29.807	-	29.605	29.605
HFA 134a	73.532	68.564	68.556	98.666	69.079	69.078

The budesonide particles in the formulations of 15, 16 and 20 sedimented.

The presence of ethanol and surfactant in the formulations improves the quality of the suspension.

Examples 12, 13 and 14 are density matched formulations employing different amounts of ethanol. Example 12 provided a stable formulation whereas the formulations of Examples 13 and 14 exhibited signs of degradation of the budesonide and crystal growth after prolonged storage.

Examples 17, 18, 19, 21 and 22 are density matched formulations. Example 22 exhibited less drug deposition than Example 21.

Examples 23 to 27

The formulations reported in the following Table were prepared in which the amounts are expressed in % w/w.

Example	23	24	25	26	27
Budesonide	0.079	0.079	0.079	0.079	0.158
Oleic Acid	-	0.001	0.004	0.008	0.001
Ethanol	1.000	1.000	1.000	1.000	1.000
HFA 227	29.676	29.676	29.675	29.674	29.652
HFA 134a	69.245	69.244	69.242	69.239	69.189

Examples 23 to 27 are density matched formulations. In the density matched formulations the floc matrix remains more evenly dispersed in the formulation than in the formulations containing HFA 134a and HFA 227 as the only propellant. Examples 24 and 25 exhibited less drug deposition than Examples 23 and 26.

Examples 28 to 31

The formulations reported in the following Table were prepared in which the amounts are expressed in w/w.

Example	28	29	30	31
Budesonide	0.328	0.323	0.321	0.318
Oleic Acid	0.001	0.001	0.001	0.001
Ethanol	1.000	1.000	1.000	1.000
HFA 227	-	9.868	14.802	19.736
HFA 134a	98.671	88.808	83.877	78.945

The formulations were compared to Example 22. Example 22 was found to provide the slowest sedimentation rate. Decreasing levels of HFA 227 resulted in more rapid sedimentation rates.

Examples 32 to 36

The formulations reported in the following Table were prepared in which all parts are by weight.

Example	32	33	34
Budesonide	0.281	0.280	0.280
Ethanol	2.500	1.000	2.500
Oleic Acid	-	0.050	0.050
HFA 227	97.219	98.670	97.170
HFA 134a	-	-	-

Example	35	36
Budesonide	0.280	0.280
Ethanol	2.500	2.500
Span 85	0.002	0.010
HFA 227	97.218	97.210

The formulations of Examples 32 to 36 creamed.

CLAIMS

1. A pharmaceutical aerosol formulation suitable for administration to a patient by oral or nasal inhalation consisting of a suspension of particulate budesonide, a hydrofluoroalkane propellant and optionally one or more of:

(i) one or more additional hydrofluoroalkane propellants

(ii) surfactant selected from oleic acid, sorbitan oleates and lecithin, and

(iii) adjuvant having a Kauri-butanol value of at least 10.

2. A pharmaceutical aerosol formulation suitable for administration to a patient by oral or nasal inhalation consisting essentially of a suspension of budesonide particles in a mixture of hydrofluoroalkane propellants and optionally one or more excipients selected from:

(i) an adjuvant having a Kauri-butanol value of at least 10,

(ii) the combination of an adjuvant (i) and a surfactant selected from oleic acid, sorbitan oleates and lecithin, and

such that the liquid mixture has a density at 20°C substantially equal to the density of budesonide.

3. A pharmaceutical aerosol formulation as claimed in Claim 1 or Claim 2 containing HFA 134a as a hydrofluoroalkane propellant.

4. A pharmaceutical aerosol formulation as claimed in Claim 1 or Claim 2 containing HFA 227 as a hydrofluoroalkane propellant.

5. A pharmaceutical aerosol formulation as claimed in any preceding Claim containing a propellant mixture of 15 to 35% by weight HFA 227 and from 65 to 85% by weight HFA 134a.

6. A pharmaceutical aerosol formulation as claimed in any preceding Claim in which the budesonide is present in an amount of from 1 to 8 mg/ml of formulation.

7. A pharmaceutical aerosol formulation as claimed in any preceding Claim containing from 0.0001 to 1% by weight of surfactant.

8. A pharmaceutical aerosol formulation as claimed in any preceding Claim containing from 0.0005 to 0.01% by weight of surfactant.

9. A pharmaceutical aerosol formulation as claimed in Claim 7 or Claim 8 in which the surfactant is oleic acid.

10. A pharmaceutical aerosol formulation as claimed in any preceding Claim containing from about 0.5% to 3.5% by weight of an adjuvant having a Kauri-butanol value of at least 10.

11. A pharmaceutical aerosol formulation as claimed in Claim 10 containing from about 1 to 2% by weight of an adjuvant having a Kauri-butanol value of at least 10.

12. A pharmaceutical aerosol formulation as claimed in Claims 9 to 11 in which the adjuvant is ethanol.

13. A pharmaceutical aerosol formulation as claimed in Claim 12 comprising about 1% by weight of ethanol.

14. A pharmaceutical aerosol formulation suitable for administration to a patient by oral or nasal inhalation consisting of:

particulate budesonide
oleic acid
ethanol
HFA 134a
HFA 227

15. A pharmaceutical aerosol formulation suitable for administration to a patient by oral or nasal inhalation consisting of:

particulate budesonide
oleic acid
ethanol
HFA 134a

16. The use of a mixture of HFA 134a and HFA 227 having a density substantially equal to the density of budesonide to suspend budesonide particles.

17. The use as claimed in Claim 16 in which said mixture is in combination with up to 1% by weight of ethanol.

18. The use as claimed in Claims 16 or 17 in which said mixture is in combination with from 0.0005 to 0.01% oleic acid.

19. A pharmaceutical product comprising an aerosol canister equipped with a metered dose dispensing valve, the canister containing a pharmaceutical aerosol formulation as claimed in any preceding Claim.

20. A method of administering budesonide to a patient comprising delivering to the patient by oral or nasal inhalation a pharmaceutical composition as claimed in any one of Claims 1 to 18.